



Prevalence and predictors of fatigue in glioblastoma: a prospective study

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Abstract: **BACKGROUND** The main goal of this study was to assess frequency, clinical correlates, and independent predictors of fatigue in a homogeneous cohort of well-defined glioblastoma patients at baseline prior to combined radio-chemotherapy. **METHODS** We prospectively included 65 glioblastoma patients at postsurgical baseline and assessed fatigue, sleepiness, mean bedtimes, mood disturbances, and clinical characteristics such as clinical performance status, presenting symptomatology, details on neurosurgical procedure, and tumor location and diameter as well as pharmacological treatment including antiepileptic drugs, antidepressants, and use of corticosteroids. Data on fatigue and sleepiness were measured with the Fatigue Severity Scale and the Epworth Sleepiness Scale, respectively, and compared with 130 age- and sex-matched healthy controls. **RESULTS** We observed a significant correlation between fatigue and sleepiness scores in both patients ($r = 0.26$; $P = .04$) and controls ($r = 0.36$; $P < .001$). Only fatigue appeared to be more common in glioblastoma patients than in healthy controls (48% vs 11%; $P < .001$) but not the frequency of sleepiness (22% vs 19%; $P = .43$). Female sex was associated with increased fatigue frequency among glioblastoma patients but not among control participants. Multiple linear regression analyses identified depression, left-sided tumor location, and female sex as strongest associates of baseline fatigue severity. **CONCLUSIONS** Our findings indicate that glioblastoma patients are frequently affected by fatigue at baseline, suggesting that factors other than those related to radio- or chemotherapy have significant impact, particularly depression and tumor localization.

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Prevalence and predictors of fatigue in glioblastoma; a prospective study

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Abstract

Background. The main goal of this study was to assess frequency, clinical correlates and independent predictors of fatigue in a homogenous cohort of well-defined glioblastoma patients at baseline prior to combined radio-chemotherapy.

Methods. We prospectively included 65 glioblastoma patients at postsurgical baseline and assessed fatigue, sleepiness, mean bedtimes, mood disturbances and clinical characteristics such as clinical performance status, presenting symptomatology, details on neurosurgical procedure, tumor location and diameter as well as pharmacologic treatment including antiepileptic drugs, antidepressants and use of corticosteroids. Data on fatigue and sleepiness were measured with the Fatigue Severity Scale and the Epworth Sleepiness Scale, respectively, and compared to 130 age- and sex-matched healthy controls.

Results. We observed a significant correlation between fatigue and sleepiness scores in both patients ($r = 0.26$, $p = 0.04$) and controls ($r = 0.36$, $p < 0.001$), but only fatigue appeared to be much more common in glioblastoma patients than in healthy controls (48% vs. 11%, $p < 0.001$), but not the frequency of sleepiness (22% vs. 19%, $p = 0.43$). Female sex was associated with increased fatigue frequency among glioblastoma patients, but not among control subjects. Multiple linear regression analyses identified depression, left-sided tumor location and female sex as strongest associates of baseline fatigue severity.

Conclusions. Our findings indicate that glioblastoma patients are frequently affected by fatigue already at baseline, suggesting that factors other than those related to radio- or chemotherapy are of significant impact, in particular depression and tumor localization.

Keywords Fatigue; glioblastoma; sleepiness; depression

Introduction

Glioblastoma is the most common primary brain tumor in adults, with an estimated incidence of about 3 per 100,000 inhabitants / year in Europe and North America.¹ The standard of care for newly diagnosed glioblastoma, subsequent to surgery, comprises radiotherapy with concomitant temozolomide followed by adjuvant temozolomide. In the study defining this treatment regimen, median survival was limited to 15 months,² and in a population-based analysis of more than 10,000 glioblastoma patients, median survival was reported to be only 12 months.³

Independent of any treatment, fatigue is a common symptom in cancer patients in general as well as in primary brain tumor patients, with an estimated prevalence of 50 to 90% and 40 to 70% respectively.^{4,5} Cancer-related fatigue is defined by the National Comprehensive Cancer Network (NCCN) as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning.⁶ The patients themselves indicate fatigue as one of the most distressing symptom related to cancer and its treatment,⁷ and it is a strong predictor of decreased patient satisfaction, health-related quality of life (QoL), and may represent one of the key reason for discontinuing treatment.⁸⁻¹⁰ Nevertheless, fatigue is believed to be underdiagnosed and underestimated in cancer patients despite its possible impact on treatment compliance.^{4,11} As a consequence, some groups have questioned, whether the standard treatment for glioblastoma is justified in view of the limited benefit on survival and the severity of associated symptoms.¹²

However, compared to other tumor types, namely breast and lung cancer, rather few studies have addressed the problem of fatigue in glioblastoma patients in depth, and several limitations have to be mentioned. First, despite large differences in underlying neurobiology, treatment procedures and prognosis, many groups have included patients with all sorts of

primary brain tumors.^{5,13} Second, baseline data are often missing, in particular in studies using a cross-sectional design.⁵ As a consequence, fatigue was mainly assessed as a treatment complication, thereby failing to acknowledge the primary impact of the tumor itself and other treatment-independent factors.¹⁴ Third, considering the advances of modern radiation techniques, the results of many older series cannot be directly compared with the current situation. Finally, while many validated fatigue questionnaires are available,^{9,15} the large majority of neurooncological studies identified and quantified fatigue in a very rudimentary way, using the Visual Analogue Scale (VAS) or one single fatigue item appearing in tools such as the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire, the M. D. Anderson Symptom Inventory–Brain Tumor Module or the Symptom Distress Scale.^{9,12,16-18}

Thus, in this prospective study we aimed at examining frequency and predictors of fatigue severity in a homogeneous cohort of glioblastoma patients at baseline prior to combined radio-chemotherapy. For this goal, we used the Fatigue Severity Scale (FSS), which has been identified as the most widely adopted fatigue questionnaire in clinical practice and has been validated for a variety of neurological diseases.^{15,19,20} In addition, we explored the evolution of fatigue, sleepiness and mood disorders during and after combined radio-chemotherapy.

Patients and Methods

This prospective, longitudinal study was conducted as a collaboration of the Departments of Neurology, Oncology and Radiation Oncology of the University Hospital of Zurich, Switzerland, between October 2008 and October 2012. The study protocol was approved by the Ethics Committee of the Canton of Zurich, Switzerland, specialized

subcommittee for Psychiatry, Neurology, Neurosurgery (Project E-43/2007), and informed consent was obtained by all patients prior to enrollment.

Patients and control subjects. We prospectively included 65 patients with newly diagnosed and histologically proven glioblastoma, corresponding to an estimated 60-65% of all eligible glioblastoma patients of the acquisition period. Patients aged ≥ 18 years undergoing postoperative standard radio-chemotherapy were eligible.² They had to be fluent in German language. The patients were examined clinically and by questionnaires at three different time points: 1) 28 ± 7 days after the initial neurosurgical procedure (1 day prior to the first radiation), 2) at the time of the last radiation and 3) prior to the initiation of the adjuvant chemotherapy. Overall, the study period captured the first ten weeks of postoperative standard treatment.

As control group we included 130 healthy and age- and sex-matched subjects using a 1:2 case-control design. The controls were selected from a previously published cohort of 454 healthy subjects, which we used in our original validation study of the German version of the Fatigue Severity Scale (FSS).¹⁹

Clinical assessment and questionnaires. Demographic variables included age, sex and educational status (defined as highest degree attained). We ascertained several tumor characteristics, including type of neurosurgical procedure (biopsy, partial, complete or unclear resection), tumor topography and brain magnetic resonance imaging based tumor diameter. To elucidate whether the presenting symptomatology affects fatigue severity, we divided the medical history in seizure, motor weakness, cognitive deficit, headache/nausea/vomiting, apathy/asthenia, visual deficit, and accidental finding. Seizure type was further classified in partial, generalized, complex-focal, and unclassified. To estimate the influence of pharmacological treatment, we included at each time point details

on anticonvulsive drugs, antidepressants, anxiolytics, CNS stimulants, hypnotics, and whether or not patients received corticosteroids, including the dose of the steroids. Clinical performance status was assessed by the Karnofsky Performance Score (KPS), with 100% indicating perfect physical health and 0% death. As mentioned earlier, we measured fatigue by means of the FSS. This self-administered questionnaire comprises 9 items exploring fatigue severity in different situations during the past week, and the final score ranges from 1 to 7, with the latter value indicating maximal fatigue. The presence of clinically significant fatigue was defined as a FSS score ≥ 4.0 . The FSS has robust psychometric properties and has been validated for various neurological disorders but not yet for glioblastoma patients. We therefore performed a reliability statistic in our cohort, revealing an excellent internal consistency as reflected by a Cronbach's α of 0.94.²¹ We used the German version of the Epworth Sleepiness Scale (ESS) for assessment of sleepiness; a score of ≥ 10 indicates EDS.²² We also determined the prevalence of overlap between fatigue and EDS, which was the case when patients presented both a FSS score ≥ 4.0 and an ESS score ≥ 10 . Sleep need was estimated using information on mean bed times. We arbitrarily defined mean bedtimes ≥ 10 hours as "long bedtimes", probably indicating increased sleep need per 24 hours (i.e. hypersomnia). Finally, for evaluation of anxiety and depression, we used the German version of the Hospital Anxiety and Depression Scale (HADS). It is a well-validated questionnaire suitable for cancer populations as it contains only nonphysical symptoms of both anxiety and depression. Participants indicate their agreement with each item on a scale ranging from 0 to 3. The questionnaire has two subscales for anxiety and depression, each consisting of 7 items. A score of > 10 is considered to indicate overt anxiety or depression.^{23,24}

Data analysis and statistics. We used SPSS (version 19.0) for statistical analysis. Group data are described by means, standard deviations (SD), and confidence intervals (95% CI). To compare mean values of FSS and ESS scores between glioblastoma patients and

control subjects, we used Student's t test; χ^2 -test was used to compare the frequency of fatigue and EDS between the two groups. Longitudinal differences of scores were assessed using Student's paired t test. We applied the Cronbach α statistics to calculate the internal consistency of the FSS in glioblastoma patients. To identify predictors of fatigue severity at baseline, we performed a multiple linear regression analysis with FSS score as dependent variable. Among the set of potential predictor variables (age, gender, education, KPS, ESS, bedtimes, anxiety and depression scores, tumor localization and use of steroids or antidepressants), we evaluated each variable for an estimated effect of ≥ 0.2 or ≤ -0.2 on the outcome score fatigue severity and a p -value < 0.05 in a univariate comparison. Those predictor variables fulfilling the two criteria were included in the multiple linear regression model. Significance was accepted at $p < 0.05$. 95% confidence intervals (CI) for mean differences between the groups were additionally presented when group differences were significantly different from zero.

Results

Characterization of glioblastoma patients. We included 65 glioblastoma patients, of whom 44 patients (68%) were male. Mean age was 57.3 ± 10.1 years. The tumor was localized in the left brain hemisphere in 28 patients (43%), in the right hemisphere in 31 patients (48%), and bilateral in 6 patients (9%). A majority of tumors affected the fronto-temporal lobes (57%) as compared to the parieto-occipital lobes (31%), basal ganglia (5%) or multiple sites (8%).

Comparison between glioblastoma patients and controls. Glioblastoma patients had significantly higher FSS scores (3.9 ± 1.7 vs. 2.8 ± 1.0 , 95% CI 0.74 - 1.49, $p < 0.001$) and fatigue frequency (48% vs. 11%, $p < 0.001$), and significantly longer bedtimes (8.8 ± 1.2 h vs.

$7.7 \pm 0.9h$, 95% CI 0.76 - 1.39, $p < 0.001$) than controls, whereas ESS scores and the prevalence of EDS was similar (Table 1). FSS and ESS scores were significantly correlated in both glioblastoma patients ($r = 0.26$, $p = 0.04$) and control subjects ($r = 0.36$, $p < 0.001$). In glioblastoma patients, overlap of both fatigue and EDS was observed in 15%, while “isolated fatigue” was much more common (32%) than “isolated EDS” (6%) (Fig. 1). Conversely, we observed more controls with “isolated EDS” (14%) than “isolated fatigue” (5%) ($p < 0.001$).

Comparison of glioblastoma patients with and without fatigue. Prior to radiotherapy, almost half of all glioblastoma patients suffered from fatigue. Compared to those without fatigue, glioblastoma patients with fatigue revealed a higher prevalence of EDS (32% vs. 12%, $p = 0.04$), spent more time in bed (95% CI 0.13 - 1.32, $p = 0.02$) and were more depressed (95% CI 0.78 - 4.04, $p = 0.005$) (Table 2). In addition, gender distribution differed significantly: of totally 21 female glioblastoma patients, 14 had fatigue (67%), while only 39% of all male patients had fatigue ($p = 0.03$). Of note, fatigue prevalence was similar in female and male controls (12% vs. 10%, $p = 0.49$). Finally, glioblastoma patients affected by a tumor in the left brain hemisphere appeared to suffer more frequently from fatigue than those with right-sided tumors (Table 3). Patients with left-sided tumor localization were also more prone to anxiety and depression. On the other hand, we did not observe any group differences concerning educational status, presenting symptomatology, seizure type, use of antiepileptic drugs or corticosteroids nor extent of tumor resection.

Predictors of fatigue severity in glioblastoma patients. Using a multiple linear regression model, we identified higher HADS-D depression score (estimated effect = 0.16 per one unit increase in depression score, $p = 0.004$), left-sided tumor location (estimated effect = -0.88, $p = 0.002$) and female sex (estimated effect 0.89, $p = 0.02$) as significant associates of fatigue

severity at baseline prior to radio-chemotherapy (Table 4). The adjusted r-squared and the multiple r-squared of our final model were 0.29 and 0.32, respectively.

Evolution of fatigue, EDS and mood disorders. Unfortunately, drop-out rate was rather high: of the included 65 GBM patients, only 46 and 38 patients filled out all questionnaires during and after radio-chemotherapy, respectively. Mean values for FSS and ESS scores, mean bedtimes, anxiety and depression scores of the HADS-D and KPS did not show significant changes at subsequent time points (Fig. 2).

Discussion

Our prospective study demonstrates that fatigue is a prominent pre-treatment symptom in patients with newly diagnosed and operated glioblastoma, reaching a prevalence of 48% compared to only 11% among healthy control subjects. Surprisingly, our data represent the first controlled assessment of fatigue frequency in a selected and homogeneous cohort of glioblastoma patients, and measured with a specific and validated fatigue questionnaire. Although direct comparison is obviously hampered by major methodological differences, our finding roughly matches the reported 40-70% fatigue prevalence among patients with primary brain tumors.^{5,9,14} On the other hand, we had found higher fatigue prevalence in patients with other neurological disorders such as multiple sclerosis (69%), idiopathic Parkinson's disease (59%), episodic migraine (54%, unpublished data) or previous ischemic stroke (49%), always using the FSS.^{19,20}

Fatigue in patients with primary brain tumors has repeatedly been reported in relation to radiotherapy.^{13,25,26} In contrast, our study challenges the view that fatigue in glioblastoma

patients represents mainly a complication of radio- and / or chemotherapy, because the prevalence of fatigue was highly already prior to radio-chemotherapy. Therefore, the contribution of toxicity from radio-chemotherapy to fatigue is probably only one single factor among many others. In addition, the longitudinal assessment of fatigue, sleepiness and mood disturbances during and after radio-chemotherapy did not show significant changes, which might reflect, however, a bias due to the high drop-out rate. On the other hand, it's conceivable that the toxic effect of radio-chemotherapy on fatigue severity was obscured in our cohort by the additional presence of many other fatigue-inducing factors. Of related interest is our observation that pharmacological treatment, including antiepileptic drugs, antidepressants or corticosteroids, was not associated with fatigue. This is in contrast to a recent work of Struik et al., who reported an increase of fatigue severity under antiepileptic drugs and corticosteroids among patients with low-grade glioma.²⁷

While fatigue was more than 4times more prevalent in glioblastoma patients than in control subjects, the frequency of excessive daytime sleepiness was similar (22% vs. 19%). Fatigue and sleepiness are commonly regarded as two distinct symptoms, but they present substantial overlap and presumably, at least to some extent, also similar pathophysiology.²⁸ Our finding is surprising, because increased frequency of sleepiness is indeed common in many neurological disorders with prominent fatigue. For instance, we found excessive daytime sleepiness in 48% of patients with idiopathic Parkinson's disease and 38% of traumatic brain injury survivors, while other groups reported an even higher prevalence.^{20,29} Degenerative or trauma-induced disruption of arousal-promoting structures in the rostral brainstem and hypothalamus may cause both fatigue and sleepiness, and this assumption is increasingly supported by neuropathological evidence.³⁰⁻³² On the other hand, fatigue is a complex symptom, influenced by a large variety of factors, and the composition of these contributing factors differs most likely between neurological disorders commonly associated

with high fatigue burden. Thus, it's tempting to speculate whether the selective increase of fatigue but normal prevalence of sleepiness may shed some light on the underlying etiology of glioblastoma-related fatigue. Of interest in this context, the discrepant prevalence of fatigue and sleepiness is reminiscent of patients with mood disorders, who often suffer from fatigue and insomnia, while sleepiness is not a consistent complaint.³³ In the same line, using multiple regression analyses we could identify depression as independent predictor of fatigue severity at baseline. To the best of our knowledge, this is the first study to highlight this important association between fatigue severity and depression in glioblastoma patients, while similar correlations have been reported in breast cancer patients but never in patients with primary brain tumors.^{34,35}

Anxiety and depression represent normal emotional reactions to the diagnosis of glioblastoma, and they are significant and independent contributors to fatigue severity. However, as emphasized by the overview of Litofsky and Resnick and further corroborated by our observations, other factors have to be considered.³⁶ Of note, fatigue, anxiety and depression all appeared to be more common in glioblastoma patients with left-sided tumors compared to those with right-sided tumors, and left-sided tumor location was consistently identified as independent predictor of fatigue severity. Indeed, there is some evidence indicating that patients with left hemispheric lesions are prone to depressive reactions, whereas patients with right hemisphere lesions often show indifferent emotional reactions.^{33,38,39} Likewise, Klein et al. found significant impairment of attentional and executive functioning in patients with left-sided high-grade glioma compared to right-sided.⁴⁰ However, several studies failed to observe any association between depression and hemispheric laterality of gliomas.⁴¹ Data on depression in ischemic stroke provide a similarly inconsistent picture. Few studies suggested a higher prevalence of depression in left-sided ischemic stroke, but other studies could not confirm a significant impact of stroke location on

depressive symptoms.⁴² Whether tumor laterality plays such a significant role in the severity of fatigue, as suggested by our study, remains to be confirmed by future work.

Similar to previous work, we found that female sex was associated with higher fatigue severity at baseline. Recently, Armstrong et al. assessed fatigue in 201 patients with primary brain tumors and demonstrated that moderate-severe fatigue was more common in females, while low fatigue was more common in males.⁵

Several limitations of our study have to be acknowledged. First, the included patient number was relatively small. Second, drop-out rates at subsequent time points were high and might have introduced significant bias. Our observations on evolution of fatigue, sleepiness and mood disorders during and after radio-chemotherapy must therefore be considered with caution and require confirmation by larger studies with minimal drop-out rates. However, elimination of a significant drop-out will be challenging, as it is a well-known, notorious problem in longitudinal studies of primary brain tumor patients. Our drop-out rate was similar, for instance, to that reported in a very recent large randomized EORTC trial.⁴³ Third, a certain selection bias is likely, as we included only 60-65% of all eligible glioblastoma patients during the study period, which prevents direct generalizability of our findings. Finally, we did not measure the impact of fatigue and associated variables on health-related quality of life.

In summary, roughly half of all glioblastoma patients are affected by fatigue at postsurgical baseline. Depression is among the strongest predictors of fatigue severity at baseline, which might also explain the unexpected absence of increased sleepiness in glioblastoma patients. Hence, treating physicians should be more vigilant with regard to fatigue and depression in glioblastoma patients, because they both represent frequent co-morbidities with mutually negative repercussions and they are known to negatively impact quality of life, treatment compliance and overall survival.^{12,16,18,44}

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Figure legends

Figure 1 Frequency and overlap of fatigue and excessive daytime sleepiness in glioblastoma patients and controls. In glioblastoma patients, fatigue is often associated with EDS, but «isolated EDS» occurs seldom.

Figure 2 Compared to postsurgical baseline, the scores of the Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), mean bedtimes, HADS-D depression and anxiety and Karnofsky Performance Score did not show any significant changes during and immediately after combined radio-chemotherapy (RCT). Error bars indicate standard deviations.

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Abstract

Background. The main goal of this study was to assess frequency, clinical correlates and independent predictors of fatigue in a homogenous cohort of well-defined glioblastoma patients at baseline prior to combined radio-chemotherapy.

Methods. We prospectively included 65 glioblastoma patients at postsurgical baseline and assessed fatigue, sleepiness, mean bedtimes, mood disturbances and clinical characteristics such as clinical performance status, presenting symptomatology, details on neurosurgical procedure, tumor location and diameter as well as pharmacologic treatment including antiepileptic drugs, antidepressants and use of corticosteroids. Data on fatigue and sleepiness were measured with the Fatigue Severity Scale and the Epworth Sleepiness Scale, respectively, and compared to 130 age- and sex-matched healthy controls.

Results. We observed a significant correlation between fatigue and sleepiness scores in both patients ($r = 0.26$, $p = 0.04$) and controls ($r = 0.36$, $p < 0.001$), but only fatigue appeared to be much more common in glioblastoma patients than in healthy controls (48% vs. 11%, $p < 0.001$), but not the frequency of sleepiness (22% vs. 19%, $p = 0.43$). Female sex was associated with increased fatigue frequency among glioblastoma patients, but not among control subjects. Multiple linear regression analyses identified depression, left-sided tumor location and female sex as strongest associates of baseline fatigue severity.

Conclusions. Our findings indicate that glioblastoma patients are frequently affected by fatigue already at baseline, suggesting that factors other than those related to radio- or chemotherapy are of significant impact, in particular depression and tumor localization.

Keywords Fatigue; glioblastoma; sleepiness; depression

Introduction

Glioblastoma is the most common primary brain tumor in adults, with an estimated incidence of about 3 per 100,000 inhabitants / year in Europe and North America.¹ The standard of care for newly diagnosed glioblastoma, subsequent to surgery, comprises radiotherapy with concomitant temozolomide followed by adjuvant temozolomide. In the study defining this treatment regimen, median survival was limited to 15 months,² and in a population-based analysis of more than 10,000 glioblastoma patients, median survival was reported to be only 12 months.³

Independent of any treatment, fatigue is a common symptom in cancer patients in general as well as in primary brain tumor patients, with an estimated prevalence of 50 to 90% and 40 to 70% respectively.^{4,5} Cancer-related fatigue is defined by the National Comprehensive Cancer Network (NCCN) as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning.⁶ The patients themselves indicate fatigue as one of the most distressing symptom related to cancer and its treatment,⁷ and it is a strong predictor of decreased patient satisfaction, health-related quality of life (QoL), and may represent one of the key reason for discontinuing treatment.⁸⁻¹⁰ Nevertheless, fatigue is believed to be underdiagnosed and underestimated in cancer patients despite its possible impact on treatment compliance.^{4,11} As a consequence, some groups have questioned, whether the standard treatment for glioblastoma is justified in view of the limited benefit on survival and the severity of associated symptoms.¹²

However, compared to other tumor types, namely breast and lung cancer, rather few studies have addressed the problem of fatigue in glioblastoma patients in depth, and several limitations have to be mentioned. First, despite large differences in underlying neurobiology, treatment procedures and prognosis, many groups have included patients with all sorts of

primary brain tumors.^{5,13} Second, baseline data are often missing, in particular in studies using a cross-sectional design.⁵ As a consequence, fatigue was mainly assessed as a treatment complication, thereby failing to acknowledge the primary impact of the tumor itself and other treatment-independent factors.¹⁴ Third, considering the advances of modern radiation techniques, the results of many older series cannot be directly compared with the current situation. Finally, while many validated fatigue questionnaires are available,^{9,15} the large majority of neurooncological studies identified and quantified fatigue in a very rudimentary way, using the Visual Analogue Scale (VAS) or one single fatigue item appearing in tools such as the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire, the M. D. Anderson Symptom Inventory–Brain Tumor Module or the Symptom Distress Scale.^{9,12,16-18}

Thus, in this prospective study we aimed at examining frequency and predictors of fatigue severity in a homogeneous cohort of glioblastoma patients at baseline prior to combined radio-chemotherapy. For this goal, we used the Fatigue Severity Scale (FSS), which has been identified as the most widely adopted fatigue questionnaire in clinical practice and has been validated for a variety of neurological diseases.^{15,19,20} In addition, we explored the evolution of fatigue, sleepiness and mood disorders during and after combined radio-chemotherapy.

Patients and Methods

This prospective, longitudinal study was conducted as a collaboration of the Departments of Neurology, Oncology and Radiation Oncology of the University Hospital of Zurich, Switzerland, between October 2008 and October 2012. The study protocol was approved by the Ethics Committee of the Canton of Zurich, Switzerland, specialized

subcommittee for Psychiatry, Neurology, Neurosurgery (Project E-43/2007), and informed consent was obtained by all patients prior to enrollment.

Patients and control subjects. We prospectively included 65 patients with newly diagnosed and histologically proven glioblastoma, corresponding to an estimated 60-65% of all eligible glioblastoma patients of the acquisition period. Patients aged ≥ 18 years undergoing postoperative standard radio-chemotherapy were eligible.² They had to be fluent in German language. The patients were examined clinically and by questionnaires at three different time points: 1) 28 ± 7 days after the initial neurosurgical procedure (1 day prior to the first radiation), 2) at the time of the last radiation and 3) prior to the initiation of the adjuvant chemotherapy. Overall, the study period captured the first ten weeks of postoperative standard treatment.

As control group we included 130 healthy and age- and sex-matched subjects using a 1:2 case-control design. The controls were selected from a previously published cohort of 454 healthy subjects, which we used in our original validation study of the German version of the Fatigue Severity Scale (FSS).¹⁹

Clinical assessment and questionnaires. Demographic variables included age, sex and educational status (defined as highest degree attained). We ascertained several tumor characteristics, including type of neurosurgical procedure (biopsy, partial, complete or unclear resection), tumor topography and brain magnetic resonance imaging based tumor diameter. To elucidate whether the presenting symptomatology affects fatigue severity, we divided the medical history in seizure, motor weakness, cognitive deficit, headache/nausea/vomiting, apathy/asthenia, visual deficit, and accidental finding. Seizure type was further classified in partial, generalized, complex-focal, and unclassified. To estimate the influence of pharmacological treatment, we included at each time point details

on anticonvulsive drugs, antidepressants, anxiolytics, CNS stimulants, hypnotics, and whether or not patients received corticosteroids, including the dose of the steroids. Clinical performance status was assessed by the Karnofsky Performance Score (KPS), with 100% indicating perfect physical health and 0% death. As mentioned earlier, we measured fatigue by means of the FSS. This self-administered questionnaire comprises 9 items exploring fatigue severity in different situations during the past week, and the final score ranges from 1 to 7, with the latter value indicating maximal fatigue. The presence of clinically significant fatigue was defined as a FSS score ≥ 4.0 . The FSS has robust psychometric properties and has been validated for various neurological disorders but not yet for glioblastoma patients. We therefore performed a reliability statistic in our cohort, revealing an excellent internal consistency as reflected by a Cronbach's α of 0.94.²¹ We used the German version of the Epworth Sleepiness Scale (ESS) for assessment of sleepiness; a score of ≥ 10 indicates EDS.²² We also determined the prevalence of overlap between fatigue and EDS, which was the case when patients presented both a FSS score ≥ 4.0 and an ESS score ≥ 10 . Sleep need was estimated using information on mean bed times. We arbitrarily defined mean bedtimes ≥ 10 hours as "long bedtimes", probably indicating increased sleep need per 24 hours (i.e. hypersomnia). Finally, for evaluation of anxiety and depression, we used the German version of the Hospital Anxiety and Depression Scale (HADS). It is a well-validated questionnaire suitable for cancer populations as it contains only nonphysical symptoms of both anxiety and depression. Participants indicate their agreement with each item on a scale ranging from 0 to 3. The questionnaire has two subscales for anxiety and depression, each consisting of 7 items. A score of > 10 is considered to indicate overt anxiety or depression.^{23,24}

Data analysis and statistics. We used SPSS (version 19.0) for statistical analysis. Group data are described by means, standard deviations (SD), and confidence intervals (95% CI). To compare mean values of FSS and ESS scores between glioblastoma patients and

control subjects, we used Student's t test; χ^2 -test was used to compare the frequency of fatigue and EDS between the two groups. Longitudinal differences of scores were assessed using Student's paired t test. We applied the Cronbach α statistics to calculate the internal consistency of the FSS in glioblastoma patients. To identify predictors of fatigue severity at baseline, we performed a multiple linear regression analysis with FSS score as dependent variable. Among the set of potential predictor variables (age, gender, education, KPS, ESS, bedtimes, anxiety and depression scores, tumor localization and use of steroids or antidepressants), we evaluated each variable for an estimated effect of ≥ 0.2 or ≤ -0.2 on the outcome score fatigue severity and a p -value < 0.05 in a univariate comparison. Those predictor variables fulfilling the two criteria were included in the multiple linear regression model. Significance was accepted at $p < 0.05$. 95% confidence intervals (CI) for mean differences between the groups were additionally presented when group differences were significantly different from zero.

Results

Characterization of glioblastoma patients. We included 65 glioblastoma patients, of whom 44 patients (68%) were male. Mean age was 57.3 ± 10.1 years. The tumor was localized in the left brain hemisphere in 28 patients (43%), in the right hemisphere in 31 patients (48%), and bilateral in 6 patients (9%). A majority of tumors affected the fronto-temporal lobes (57%) as compared to the parieto-occipital lobes (31%), basal ganglia (5%) or multiple sites (8%).

Comparison between glioblastoma patients and controls. Glioblastoma patients had significantly higher FSS scores (3.9 ± 1.7 vs. 2.8 ± 1.0 , 95% CI 0.74 - 1.49, $p < 0.001$) and fatigue frequency (48% vs. 11%, $p < 0.001$), and significantly longer bedtimes (8.8 ± 1.2 h vs.

7.7 ± 0.9 h, 95% CI 0.76 - 1.39, $p < 0.001$) than controls, whereas ESS scores and the prevalence of EDS was similar (Table 1). FSS and ESS scores were significantly correlated in both glioblastoma patients ($r = 0.26$, $p = 0.04$) and control subjects ($r = 0.36$, $p < 0.001$). In glioblastoma patients, overlap of both fatigue and EDS was observed in 15%, while “isolated fatigue” was much more common (32%) than “isolated EDS” (6%) (Fig. 1). Conversely, we observed more controls with “isolated EDS” (14%) than “isolated fatigue” (5%) ($p < 0.001$).

Comparison of glioblastoma patients with and without fatigue. Prior to radiotherapy, almost half of all glioblastoma patients suffered from fatigue. Compared to those without fatigue, glioblastoma patients with fatigue revealed a higher prevalence of EDS (32% vs. 12%, $p = 0.04$), spent more time in bed (95% CI 0.13 - 1.32, $p = 0.02$) and were more depressed (95% CI 0.78 - 4.04, $p = 0.005$) (Table 2). In addition, gender distribution differed significantly: of totally 21 female glioblastoma patients, 14 had fatigue (67%), while only 39% of all male patients had fatigue ($p = 0.03$). Of note, fatigue prevalence was similar in female and male controls (12% vs. 10%, $p = 0.49$). Finally, glioblastoma patients affected by a tumor in the left brain hemisphere appeared to suffer more frequently from fatigue than those with right-sided tumors (Table 3). Patients with left-sided tumor localization were also more prone to anxiety and depression. On the other hand, we did not observe any group differences concerning educational status, presenting symptomatology, seizure type, use of antiepileptic drugs or corticosteroids nor extent of tumor resection.

Predictors of fatigue severity in glioblastoma patients. Using a multiple linear regression model, we identified higher HADS-D depression score (estimated effect = 0.16 per one unit increase in depression score, $p = 0.004$), left-sided tumor location (estimated effect = -0.88, $p = 0.002$) and female sex (estimated effect 0.89, $p = 0.02$) as significant associates of fatigue

severity at baseline prior to radio-chemotherapy (Table 4). The adjusted r-squared and the multiple r-squared of our final model were 0.29 and 0.32, respectively.

Evolution of fatigue, EDS and mood disorders. Unfortunately, drop-out rate was rather high: of the included 65 GBM patients, only 46 and 38 patients filled out all questionnaires during and after radio-chemotherapy, respectively. Mean values for FSS and ESS scores, mean bedtimes, anxiety and depression scores of the HADS-D and KPS did not show significant changes at subsequent time points (Fig. 2).

Discussion

Our prospective study demonstrates that fatigue is a prominent pre-treatment symptom in patients with newly diagnosed and operated glioblastoma, reaching a prevalence of 48% compared to only 11% among healthy control subjects. Surprisingly, our data represent the first controlled assessment of fatigue frequency in a selected and homogeneous cohort of glioblastoma patients, and measured with a specific and validated fatigue questionnaire. Although direct comparison is obviously hampered by major methodological differences, our finding roughly matches the reported 40-70% fatigue prevalence among patients with primary brain tumors.^{5,9,14} On the other hand, we had found higher fatigue prevalence in patients with other neurological disorders such as multiple sclerosis (69%), idiopathic Parkinson's disease (59%), episodic migraine (54%, unpublished data) or previous ischemic stroke (49%), always using the FSS.^{19,20}

Fatigue in patients with primary brain tumors has repeatedly been reported in relation to radiotherapy.^{13,25,26} In contrast, our study challenges the view that fatigue in glioblastoma

patients represents mainly a complication of radio- and / or chemotherapy, because the prevalence of fatigue was highly already prior to radio-chemotherapy. Therefore, the contribution of toxicity from radio-chemotherapy to fatigue is probably only one single factor among many others. In addition, the longitudinal assessment of fatigue, sleepiness and mood disturbances during and after radio-chemotherapy did not show significant changes, which might reflect, however, a bias due to the high drop-out rate. On the other hand, it's conceivable that the toxic effect of radio-chemotherapy on fatigue severity was obscured in our cohort by the additional presence of many other fatigue-inducing factors. Of related interest is our observation that pharmacological treatment, including antiepileptic drugs, antidepressants or corticosteroids, was not associated with fatigue. This is in contrast to a recent work of Struik et al., who reported an increase of fatigue severity under antiepileptic drugs and corticosteroids among patients with low-grade glioma.²⁷

While fatigue was more than 4times more prevalent in glioblastoma patients than in control subjects, the frequency of excessive daytime sleepiness was similar (22% vs. 19%). Fatigue and sleepiness are commonly regarded as two distinct symptoms, but they present substantial overlap and presumably, at least to some extent, also similar pathophysiology.²⁸ Our finding is surprising, because increased frequency of sleepiness is indeed common in many neurological disorders with prominent fatigue. For instance, we found excessive daytime sleepiness in 48% of patients with idiopathic Parkinson's disease and 38% of traumatic brain injury survivors, while other groups reported an even higher prevalence.^{20,29} Degenerative or trauma-induced disruption of arousal-promoting structures in the rostral brainstem and hypothalamus may cause both fatigue and sleepiness, and this assumption is increasingly supported by neuropathological evidence.³⁰⁻³² On the other hand, fatigue is a complex symptom, influenced by a large variety of factors, and the composition of these contributing factors differs most likely between neurological disorders commonly associated

with high fatigue burden. Thus, it's tempting to speculate whether the selective increase of fatigue but normal prevalence of sleepiness may shed some light on the underlying etiology of glioblastoma-related fatigue. Of interest in this context, the discrepant prevalence of fatigue and sleepiness is reminiscent of patients with mood disorders, who often suffer from fatigue and insomnia, while sleepiness is not a consistent complaint.³³ In the same line, using multiple regression analyses we could identify depression as independent predictor of fatigue severity at baseline. To the best of our knowledge, this is the first study to highlight this important association between fatigue severity and depression in glioblastoma patients, while similar correlations have been reported in breast cancer patients but never in patients with primary brain tumors.^{34,35}

Anxiety and depression represent normal emotional reactions to the diagnosis of glioblastoma, and they are significant and independent contributors to fatigue severity. However, as emphasized by the overview of Litofsky and Resnick and further corroborated by our observations, other factors have to be considered.³⁶ Of note, fatigue, anxiety and depression all appeared to be more common in glioblastoma patients with left-sided tumors compared to those with right-sided tumors, and left-sided tumor location was consistently identified as independent predictor of fatigue severity. Indeed, there is some evidence indicating that patients with left hemispheric lesions are prone to depressive reactions, whereas patients with right hemisphere lesions often show indifferent emotional reactions.^{33,38,39} Likewise, Klein et al. found significant impairment of attentional and executive functioning in patients with left-sided high-grade glioma compared to right-sided.⁴⁰ However, several studies failed to observe any association between depression and hemispheric laterality of gliomas.⁴¹ Data on depression in ischemic stroke provide a similarly inconsistent picture. Few studies suggested a higher prevalence of depression in left-sided ischemic stroke, but other studies could not confirm a significant impact of stroke location on

depressive symptoms.⁴² Whether tumor laterality plays such a significant role in the severity of fatigue, as suggested by our study, remains to be confirmed by future work.

Similar to previous work, we found that female sex was associated with higher fatigue severity at baseline. Recently, Armstrong et al. assessed fatigue in 201 patients with primary brain tumors and demonstrated that moderate-severe fatigue was more common in females, while low fatigue was more common in males.⁵

Several limitations of our study have to be acknowledged. First, the included patient number was relatively small. Second, drop-out rates at subsequent time points were high and might have introduced significant bias. Our observations on evolution of fatigue, sleepiness and mood disorders during and after radio-chemotherapy must therefore be considered with caution and require confirmation by larger studies with minimal drop-out rates. However, elimination of a significant drop-out will be challenging, as it is a well-known, notorious problem in longitudinal studies of primary brain tumor patients. Our drop-out rate was similar, for instance, to that reported in a very recent large randomized EORTC trial.⁴³ Third, a certain selection bias is likely, as we included only 60-65% of all eligible glioblastoma patients during the study period, which prevents direct generalizability of our findings. Finally, we did not measure the impact of fatigue and associated variables on health-related quality of life.

In summary, roughly half of all glioblastoma patients are affected by fatigue at postsurgical baseline. Depression is among the strongest predictors of fatigue severity at baseline, which might also explain the unexpected absence of increased sleepiness in glioblastoma patients. Hence, treating physicians should be more vigilant with regard to fatigue and depression in glioblastoma patients, because they both represent frequent co-morbidities with mutually negative repercussions and they are known to negatively impact quality of life, treatment compliance and overall survival.^{12,16,18,44}

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Figure legends

Figure 1 Frequency and overlap of fatigue and excessive daytime sleepiness in glioblastoma patients and controls. In glioblastoma patients, fatigue is often associated with EDS, but «isolated EDS» occurs seldom.

Figure 2 Compared to postsurgical baseline, the scores of the Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), mean bedtimes, HADS-D depression and anxiety and Karnofsky Performance Score did not show any significant changes during and immediately after combined radio-chemotherapy (RCT). Error bars indicate standard deviations.

Table 1 Comparison of frequency and severity of fatigue, sleepiness and mean bedtimes between glioblastoma patients and controls. Values are mean ± standard deviation.

	Glioblastoma patients (n = 65)	Controls (n = 130)	<i>p</i>
Age [y]	57.3 ± 10.1	57.4 ± 9.8	0.93
Gender, male	44 (68%)	88 (68%)	0.57
FSS	3.9 ± 1.7	2.8 ± 1.0	<0.001
Fatigue (FSS >4.0)	31 (48%)	14 (11%)	<0.001
ESS	5.9 ± 4.3	6.2 ± 3.6	0.67
EDS (ESS > 10)	14 (22%)	25 (19%)	0.43
Mean bedtime [h]	8.8 ± 1.2	7.7 ± 0.9	<0.001
Long bedtime (>10h)	10 (16%)	4 (3%)	0.003

EDS: excessive daytime sleepiness

ESS: Epworth Sleepiness Scale

FSS: Fatigue Severity Scale

Table 2 Comparison of glioblastoma patients with and without fatigue at baseline. Data are described as mean \pm standard deviation.

	Glioblastoma patients with fatigue (n = 31)	Glioblastoma patients without fatigue (n = 34)	<i>p</i>
Age [y]	57.4 \pm 10.6	57.2 \pm 9.7	0.94
Male : Female	17 (55%) : 14 (45%)	27 (79%) : 7 (21%)	0.03
KPS	82.2 \pm 15.1	85.5 \pm 11.3	0.36
Tumor diameter [cm]	4.0 \pm 1.5	4.0 \pm 1.5	0.84
<u>Tumor localization</u>			0.03
Left	19 (61%)	9 (26%)	
Right	12 (39%)	19 (56%)	
Bilateral	0	6 (18%)	
<u>Tumor topography</u>			0.59
Fronto-temporal	20	17	
Parieto-occipital	7	13	
Basal ganglia	1	2	
Fronto-temporal + parieto-occ.	3	1	
Parieto-occ. + basal ganglia	0	1	
<u>Presenting symptomatology</u>			0.18

Seizure	15	15	
Motor weakness	5	7	
Cognitive deficit	8	7	
Headache, nausea, vomiting	8	5	
Apathy, asthenia	0	2	
Visual deficit	0	3	
Accidental finding	0	1	
<u>Seizure type</u>			0.63
No seizure	6	12	
Partial	4	5	
Generalized	9	8	
Complex-focal	2	0	
Unclassified	1	1	
Partial + generalized	2	3	
Complex-focal + generalized	0	1	
<u>Antiepileptic drugs</u>	19	22	0.49
Levetiracetam	9	12	
Phenytoin	9	7	
Clobazam	5	6	
Lamotrigin	2	3	
Clonazepam	1	0	
Topiramate	1	0	
Gabapentin	0	2	
Valproate	1	1	

<u>Extent of resection</u>			0.74
Biopsy	2	4	
Partial	22	20	
Complete	6	8	
Unclear	1	2	
ESS score	7.1 ± 4.9	4.8 ± 3.4	0.03
EDS (ESS score >10)	10 (32%)	4 (12%)	0.04
Mean bedtime [h]	9.2 ± 1.2	8.5 ± 1.1	0.02
Long bedtime (>10h)	6 (19%)	4 (12%)	0.25
Anxiety score	6.2 ± 4.0	5.3 ± 3.7	0.32
Anxiety, prevalence	7 (23%)	4 (18%)	0.20
Depression score	5.7 ± 3.5	3.3 ± 3.1	0.005
Depression, prevalence	4 (13%)	2 (6%)	0.29
Corticosteroids [mg]	2.7 ± 3.7	2.5 ± 2.7	0.79
Activating antidepressants	3	2	0.46
Sedating antidepressants	1	1	0.73
Anxiolytics	0	0	
CNS stimulants	0	0	
Hypnotics	1	2	0.54

EDS: excessive daytime sleepiness

ESS: Epworth Sleepiness Scale

FSS: Fatigue Severity Scale

KPS: Karnofsky performance status

Table 3 Comparison of fatigue, sleepiness and mood disorders between patients with left- and right-sided glioblastoma at baseline prior to radio-chemotherapy.

Data are described as mean ± standard deviation.

	Left-sided tumor (n = 28)	Right-sided tumor (n = 31)	p
Age [y]	55.8 ± 9.5	57.9 ± 10.5	0.43
Gender, male	20 (71%)	21 (68%)	0.60
Karnofsky performance status	86 ± 14	83 ± 12	0.40
Tumor diameter [cm]	4.0 ± 1.7	4.0 ± 1.3	0.92
FSS	4.6 ± 1.3	3.5 ± 1.8	0.008
Fatigue (FSS >4.0)	19 (68%)	12 (39%)	0.004
ESS	5.8 ± 4.2	6.0 ± 4.7	0.83
EDS (ESS >10)	5 (18%)	8 (26%)	0.73
Mean bedtime [h]	9.1 ± 1.4	8.6 ± 1.0	0.13
Long bedtime (>10h)	7 (25%)	3 (11)	0.18
Anxiety, HADS-D	6.6 ± 3.8	5.1 ± 4.0	0.16
Anxiety (prevalence)	8 (30%)	3 (10%)	0.03
Depression, HADS-D	5.3 ± 2.9	3.6 ± 3.8	0.05
Depression, prevalence	2 (9%)	4 (13%)	0.49

EDS: excessive daytime sleepiness

ESS: Epworth Sleepiness Scale

FSS: Fatigue Severity Scale

HADS-D: Hospital Anxiety and Depression Scale, German version

Table 4 Multiple linear regression model for coefficients of fatigue severity at baseline in glioblastoma patients.

<i>Dependent variable</i>	Significant coefficients *	Estimated effect	Standard error	t value	<i>p</i>
<i>FSS score (baseline)</i>	HADS-D score for depression	0.16	0.05	3.03	0.004
	Tumor localization [left]	0.88	0.28	3.16	0.002
	Female sex	0.89	0.38	2.38	0.020

* Additional coefficients included in the model were age, education, Karnofsky Performance Score, Epworth Sleepiness Scale, bedtimes, HADS-D score for anxiety, use of steroids, and use of antidepressants.

FSS: Fatigue Severity Scale

HADS-D: Hospital Anxiety and Depression Scale, German version

Figure

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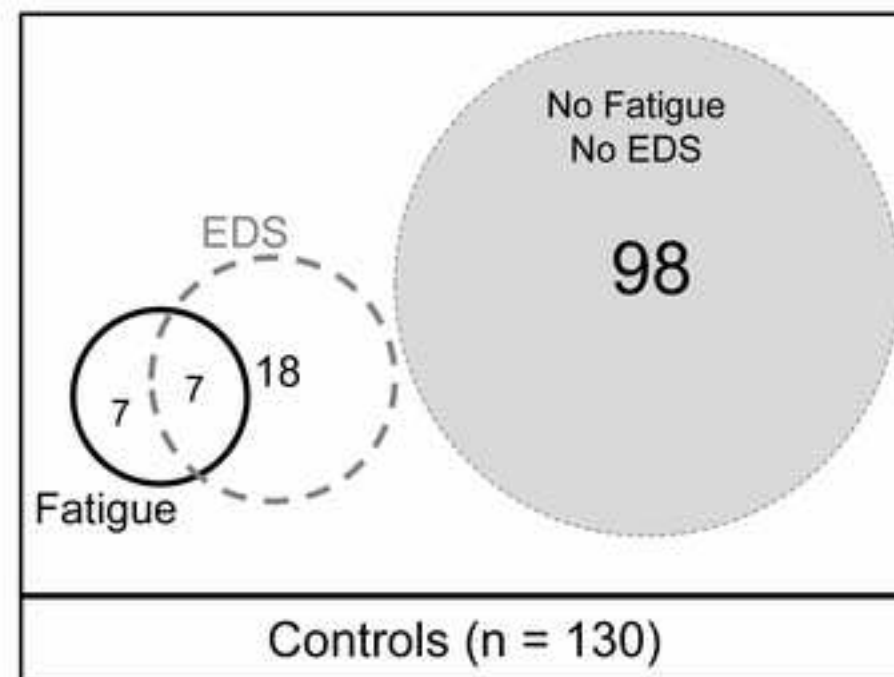
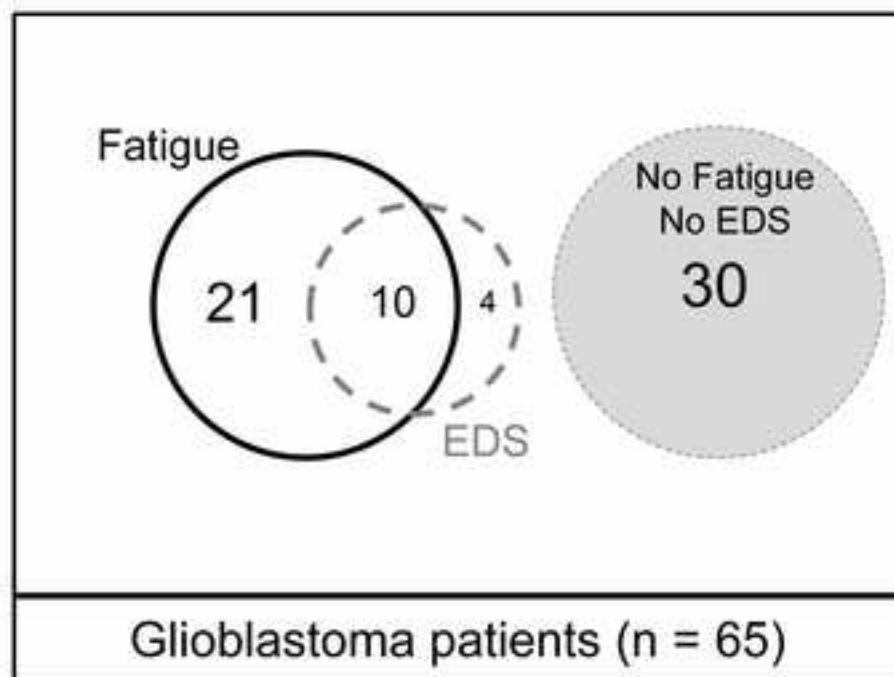


Figure
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